Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling: Current Opinion

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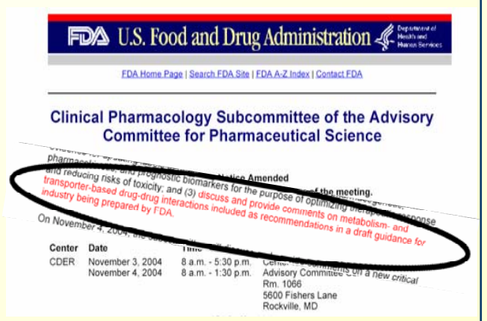
PURPOSE

• Creation of a concept paper that reflects the Agency's current view that the metabolism of a new drug should be defined and its potential to interact with other drugs should be explored as part of the assessment of safety and effectiveness.

METHODS

• Latest scientific consensus on drug metabolism, drug transporters and pharmacokinetics was considered, based on discussions at conferences, advisory committee meetings, and consultation with experts.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Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science

...transporter-based drug-drug interactions included as recommendations in a draft guidance for industry being prepared by FDA.

Center	Date	Time
CDER	November 3, 2004	8 a.m. - 5:30 p.m.
	November 4, 2004	8 a.m. - 1:30 p.m.

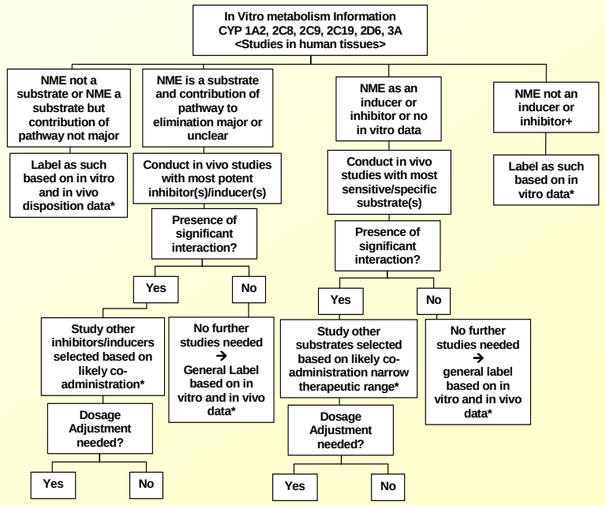
Advisory Committee for a new critical
Rm. 1066
5600 Fishers Lane
Rockville, MD


Drug Interaction Working Group Members

RESULTS

In Vitro Methods

•Evaluation of drug interactions involves an integration of *in vitro* and *in vivo* methods, as indicated by the decision tree in the concept paper.



NME: New molecular entity

* Additional population pharmacokinetic analysis may assist the overall evaluation

In Vivo Methods

•Concept paper includes details of study design and a list of marker *in vivo* CYP substrates, inhibitors and inducers.

Examples of *in vivo* substrate, inhibitor, and inducer for specific CYP enzymes recommended for study

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	smoking
2B6	efavirenz		rifampin
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone (use of PM subjects)	rifampin
2C19	omeprazole, esomeprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide (use of PM subjects)	rifampin
2D6	desipramine, dextromethorphan, atomoxetine	paroxetine, quinidine, (use of PM subjects)	none identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole	rifampin, carbamazepine

Substrates are drugs with > 2-fold increase (>5-fold for CYP3A only) in plasma AUC values when coadministered with inhibitors of that CYP enzyme.
Inhibitors are those that cause a > 2-fold increase (>5-fold for CYP3A substrates only) in plasma AUC values of substrates for that CYP enzyme.
Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by **30% or higher**.

In Vitro Methods

•Concept paper describes principles of study conduct, including up to date information on *in vitro* induction studies. A list of marker CYP substrates, inhibitors and inducers is provided. Paper indicates specific results from *in vitro* studies that warrant *in vivo* investigation.

CYP Substrates

CYP	Substrate & Reaction Preferred	Km (μM)	Substrate & Reaction Acceptable	Km (μM)
1A2	phenacetin-O-deethylation	1.7 – 152	7-ethoxyresorufin-O-deethylation theophylline-N-demethylation caffeine-3-N-demethylation tacrine 1-hydroxylation	0.18 – 0.21 280 – 1230 220 – 1565 2.8, 16
2A6	coumarin-7-hydroxylation nicotine C-oxidation	0.30 – 2.3 13 – 162		
2B6	efavirenz hydroxylase	17 – 23	propofol hydroxylation S-mephenytoin-N-demethylation bupropion-hydroxylation	3.7 – 94 1910 67 – 168
2C8	paclitaxel 6α-hydroxylation	5.4 – 19	amodiaquine N-deethylation rosiglitazone para-hydroxylation	2.4, 4.3 – 7.7
2C9	tolbutamide methyl-hydroxylation S-warfarin 7-hydroxylation diclofenac 4'-hydroxylation	67 – 838 1.5 – 4.5 3.4 – 52	flurbiprofen 4'-hydroxylation phenytoin-4-hydroxylation	6 – 42 11.5 – 117
2C19	S-mephenytoin 4'-hydroxylation	13 – 35	omeprazole 5-hydroxylation fluoxetine O-dealkylation	17 – 26 3.7 – 104
2D6	(±)-bufuralol 1'-hydroxylation dextromethorphan O-demethylation	9 – 15 0.44 – 8.5	debrisoquine 4-hydroxylation	5.6
2E1	chlorzoxazone 6-hydroxylation	39 – 157	p-nitrophenol 3-hydroxylation lauric acid 11-hydroxylation aniline 4-hydroxylation	3.3 130 6.3 – 24
3A4/5	midazolam 1-hydroxylation testosterone 6β-hydroxylation	1 – 14 52 – 94	erythromycin N-demethylation dextromethorphan N-demethylation triazolam 4-hydroxylation terfenadine C-hydroxylation nifedipine oxidation	33 – 88 133 – 710 234 15 5.1 – 47

CYP Inhibitors

CYP	Inhibitor Preferred	Ki (μM)	Inhibitor Acceptable	Ki (μM)
1A2	furafylline	0.6 – 0.73	α-naphthoflavone	0.01
2A6	tranylcypromine methoxsalen	0.02 – 0.2 0.01 – 0.2	pilocarpine tryptamine	4 1.7
2B6			3-isopropenyl-3-methyl diamantane 2-isopropenyl-2-methyl adamantane sertraline phencyclidine triethylenethiophosphoramide (thiotepa) clopidogrel ticlopidine	2.2 5.3 3.2 10 4.8 0.5 0.2
2C8	quercetin	1.1	trimethoprim gemfibrozil rosiglitazone pioglitazone	32 69 – 75 5.6 1.7
2C9	sulfaphenazole	0.3	fluconazole fluvoxamine fluoxetine	7 6.4 – 19 18 – 41
2C19			ticlopidine nootkatone	1.2 0.5
2D6	quinidine	0.027 – 0.4		
2E1			diethyldithiocarbamate clomethiazole diallyldisulfide	9.8 – 34 12 150
3A4/5	ketoconazole itraconazole	0.0037 – 0.18 0.27, 2.3	troleandomycin verapamil	17 10, 24

CYP Inducers

CYP	Inducer Preferred	Inducer (μM)	Fold Induction	Inducer Acceptable	Inducer (μM)	Fold Induction
1A2	omeprazole 8-naphthoflavone 3-methylcholanthrene	25-100 33-50 1.2	14-24 4-23 6-26	lansoprazole	10	10
2A6	Dexamethasone	50	9.4	pyrazole	1000	7.7
2B6	Phenobarbital	500-1000	5-10	phenytoin	50	5-10
2C8	Rifampin	10	2-4	phenobarbital	500	2-3
2C9	Rifampin	10	3.7	phenobarbital	100	2.6
2C19	Rifampin	10	20			
2D6	none identified					
2E1	none identified					
3A4	rifampin	10-50	4-31	Phenobarbital phenytoin rifapentine troglitazone taxol dexamethasone	100-2000 50 50 10-75 4 33-250	3-31 12.5 9.3 7 5.2 2.9- 6.9

Prediction of Clinical Relevance of Competitive CYP Inhibition

➢A follow-up *in vivo* evaluation is recommended if an estimated I/Ki ratio > 0.1.
➢[I] represents the mean steady-state C_{max} for the highest proposed clinical dose.
➢Note: Potential for a drug to inhibit CYP3A should be evaluated employing two structurally unrelated substrates. If any one of the two evaluations meet the above criteria, an *in vivo* study is recommended.

Prediction of Clinical Relevance of CYP Induction

➢In vivo evaluation is warranted if a drug produces a fold-change in CYP enzyme activity > 40% of the positive control *in vitro*.
➢If a test drug is not an inducer of CYP3A4, *in vitro*, then it can be assumed to be non-inducer of CYP2C9 or CYP2C19.

•*In vitro* studies that evaluate the potential for interactions related to drug transporters, particularly P-glycoprotein, are described.

➢Lists of marker P-gp substrates and inhibitors are provided.
➢Decision trees and criteria are provided to determine if a test compound is a substrate or an inhibitor for P-gp, and whether an *in vivo* drug interaction study is needed.

In Vivo Methods

•Concept paper also includes recommendations on the conduct of *in vivo* P-glycoprotein inhibition related interactions.

➢Testing an investigational drug as P-gp substrate:
  ➢If it is a CYP3A substrate:
  It may be appropriate to use a dual inhibitor of both CYP3A and P-gp, such as ritonavir.
  ➢If it is not a substrate of CYP3A:
  It may be appropriate to use a strong inhibitor of P-gp, such as cyclosporine or verapamil.
➢Investigation of a drug as a potential P-gp inhibitor may require digoxin or other known substrates of P-gp.

Labeling Implications

•The labeling discussion includes a list of sensitive substrates and potent and moderate inhibitors for all major CYPs to help make labeling recommendations more consistent. (Only lists pertinent to CYP3A are presented here)

➢If a drug is a **strong inhibitor** of CYP3A:
  ➢A warning will be issued about a drug interaction with all sensitive CYP3A substrates and CYP3A substrates with narrow therapeutic index.
➢If a drug is a **sensitive substrate** of CYP3A or a CYP3A substrate with a narrow therapeutic index:
  ➢It need not be tested with all strong or moderate inhibitors of CYP3A
  ➢A warning will be issued about an interaction with a list of strong or moderate CYP3A inhibitors.
  ➢It need not be tested with all CYP3A inducers
  ➢A warning will be issued about an interaction with CYP3A inducers. Examples of CYP3A inducers include rifampin, rifabutin, rifapentin, dexamethasone, phenytoin, carbamazepine, phenobarbital, and St. John's Wort.

Sensitive CYP3A substrates	CYP3A Substrates with Narrow therapeutic range
budesonide, buspirone, eplerenone, eletriptan, felodipine, imatinab, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	alfentanil, astemizole, cisapride, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Mild CYP3A inhibitors
≥ 5-fold increase in AUC	***≥ 2 but <5-fold increase in AUC***	***> 1.25 but <2-fold increase in AUC***
atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole	amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosaprenavir, grapefruit juice(a), verapamil	roxithromycin

SUMMARY AND CONCLUSIONS

• The concept paper includes current recommendations for *in vitro* and *in vivo* drug metabolism and drug interaction studies performed during drug development. The decision tree shown above emphasizes the integrated approach to evaluation of drug interactions.

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